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Congenital Hypertrichosis, Osteochondrodysplasia, and Cardiomegaly: Further Delineation of a New Genetic Syndrome

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The hypertrichosis and osteochondrodysplasia syndrome is a rare entity with clinical findings including macrosomia at birth cardiomegaly. Autosomal recessive inheritance is presumed based on the report of two affected sibs born to healthy parents. Here we report on four new patients with their follow-up data, as well as on one of the four cases from the original report. Comparison of all eight cases indicates that they share 50% of clinical and radiological changes. This report contributes to the further delineation of this newly recognized syndrome. Am. J. Med. Genet. 69:138–151, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: autosomal recessive; cardiomegaly; congenital; hypertrichosis; macrosomia; osteochondrodysplasia; pericarditis

INTRODUCTION

A syndrome characterized by hypertrichosis and osteochondrodysplasia was described by Cantú et al. [1982]. Clinical findings include congenital generalized hypertrichosis, macrosomia at birth, and cardiomegaly. Autosomal recessive inheritance is presumed based on the birth of two affected sibs to healthy parents (MIM 239850) [McKusick, 1994].

The purpose of this report is to describe 5 patients with this new syndrome with follow-up data also to include one of the original cases and to further delineate the entity.

CLINICAL REPORTS

Patient A

The propositus, age 15 years (Fig. 1), was the product of the mother's fifth term uncomplicated pregnancy and normal delivery. Birthweight was 5,800 g and the child presented with neonatal cyanosis. There was evident macrocephaly with generalized hirsutism. At age 6 months, cardiopathy and hypothyroidism were suspected; the former was confirmed and the latter ruled out by normal thyroid function tests. At 15 years, growth was normal (Table I). Clinical findings are in Table II and include hypermobility of the interphalangeal joints in both hands. The radiological findings are in Table III and Figures 2–4.

Oral examination showed mixed dentition, anterior open bite, lateral collapse, posterior and anterior crossbite, Angle's Class II molar relationship, lower crowded teeth, and anterior and low-set tongue.

Follow-up of the propositus since the age of 7 years (Fig. 2) showed progression of the following roentgenologic findings directly related to age: narrow thorax, platyspondyly, irregularities of the articular surfaces of the vertebral bodies, bilateral coxa

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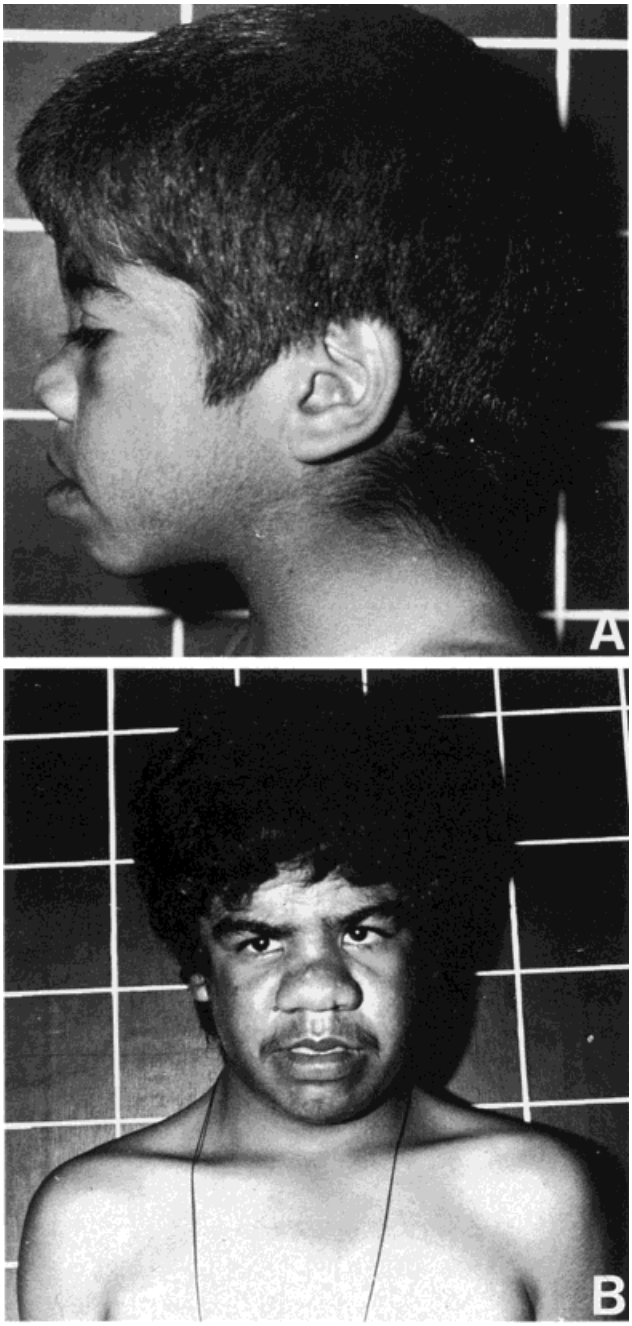

Fig. 1. Patient A at age 7 years. Note: (**A**) Flat nasal bridge, abundant eyebrows and eyelashes, long philtrum, prominent lips, retromicrognathia, and the hypertrichosis distributed from forehead to the nape of the neck and the back. At 15 years, note (**B**) coarse facial characteristics, with telecanthus, bilateral epicanthal folds, and thick lips. The body hypertrichosis is remarkably decreased, although persistent on the face.

TABLE I. Quantitative Clinical Data

Parameters	Patient A	Patient B	Patient C	Patient D
Age (years)	15	16	6 3/12	3 5/12
Birthweight (g)	5,800	2,000[a]	3,300	3,100[b]
Height (cm)	159	165	113	87 (97p)
Weight (kg)	58.5	64.5	28.5 (>97[c])	12
OFC (cm)	58	60.5	53.5 (>97[c])	55 (>97[c])
I.Q.	70	62	2-10/12[c]	7/12[d]

[a] Unspecified gestational age.
[b] 35–36 weeks of gestation.
[c] Developmental quotient (D.Q.) at age 3 years.
[d] Developmental quotient (D.Q.) at age 11 months.

valga, broad medullary canal (more evident in the tibiae), bands of growth arrest, and delayed bone age. The vertebral bodies at an early age were ovoid-shaped, becoming cuboid at puberty (Figs. 2–4).

The cardiological evaluation showed a systolic and diastolic murmurs in the left paraesternal region; echocardiography showed a bicuspid aortic valve. At 8 years of age, an echocardiogram showed concentric hypertrophy of the left ventricle. An EEG showed encephalopathic changes. Psychological evaluation indicated an IQ of 70.

The laboratory examination including routine blood and urine tests, and screening tests for metabolic defects gave normal or negative results.

The mother and fatehr were healthy and nonconsanguineous, age 29 and 37 years at the propositus' birth, respectively. A sister and a brother and 2 deceased sibs (one of omphalitis and the other of bronchopneumonia) were described as clinically normal.

Patient B

The propositus, age 16 years (Figs. 5–6), was the product of a first pregnancy of unknown gestational length. Delivery was by Caesarean section. The infant presented with neonatal cyanosis. Birthweight was 2,000 g; length was not recorded but referred to as short. Since birth, mother noticed excessive facial hairiness, synophrys, and hypertrichosis moderately distributed on trunk and limbs. The propositus experienced diarrhea during the first 3 years. At 6 years, the excess hair stopped growing. The propositus was first referred because of the hypertrichosis as an abundant mustache began to grow at 12 years of age. His psychomotor development was mildly delayed, and a psychological evaluation showed an IQ of 62.

The physical and clinial data are shown in Tables I and II, respectively; growth parameters were normal, except the OFC, which was above the 97th centile. Additionally, he presented with a narrow forehead, broad

TABLE II. Comparative Clinical Findings

	Patient A	Patient B	Patient C	Patient D	Previous cases including Patient E	Total
Congenital hypertrichosis	+	+	+	+	4/4	8/8
Coarse facial face	+	+	+	+	4/4	8/8
Macrocephaly	+	+	+	+	0/4	4/8
Abundant eyebrows and curly eyelashes	+	+	+	+	4/4	8/8
Epicanthal folds	+	−	+	+	3/4	6/8
Flat/broad nasal bridge	+	−	+	+	2/4	5/8
Small nose	−	−	−	+	2/4	3/8
Anteverted nostrils	+	−	+	+	3/4	6/8
Prominent mouth	+	+	−	+	4/4	7/8
Long philtrum	+	+	+	+	3/4	7/8
Short neck	+	+	−	−	4/4	6/8
Narrow shoulders	−	−	+	−	4/4	5/7
Narrow thorax	−	−	−	+	4/4	5/8
Short and broad first toe	−	−	+	−	3/4	4/8
Congenital concentric hypertrophy of left ventricle	+	−	−	−	1/4	2/8
Pericarditis with effusion	−	−	−	−	1/4	1/8
Primary lymphedema	−	−	−	−	1/4	1/8
Macrosomia at birth	+	−	−	+	3/4	5/8
Mild mental retardation	+	+	−	+	1/4	4/8

TABLE III. Comparative Radiological Findings

	Patient A	Patient B	Patient C	Patient D	Previous cases including Patient E	Total
Enlarged posterior fossa and vertical base of cranium	+	+	+	+	1/4	5/8
Global cardiomegaly	+	+	+	+	4/4	8/8
Wide ribs	−	−	+	+	4/4	6/8
Platyspondyly	−	−	+	+	4/4	6/8
Irregularities on surface of vertebral bodies	−	−	+	+	1/4	3/8
Ovoid-shape vertebral bodies	+	+	−		1/4	3/7
Cuboid-shape vertebral bodies at puberty/adulthood	+	+	−	−	1/4	3/8
Hypoplastic ischiopubic branches	+	+	−		4/4	6/7
Narrow obturator foramen	−	+	−	−	4/4	5/8
Bilateral coxa valga	+	+	−	+	4/4	7/8
"Erlenmeyer flask" shaped long bones and enlarged medullary canal	+	+	+	+	4/4	8/8
Generalized osteopenia	+	−	−	−	4/4	5/8
Bands of growth arrest	+	−	+	+	4/4	7/8
Shortening of distal phalanx of thumbs and first toes	−	−	+	+	4/4	6/8
Broadened first metatarsal	+	+	+	+	4/4	8/8
Delayed bone age	+	+	−	−	3/4	5/8

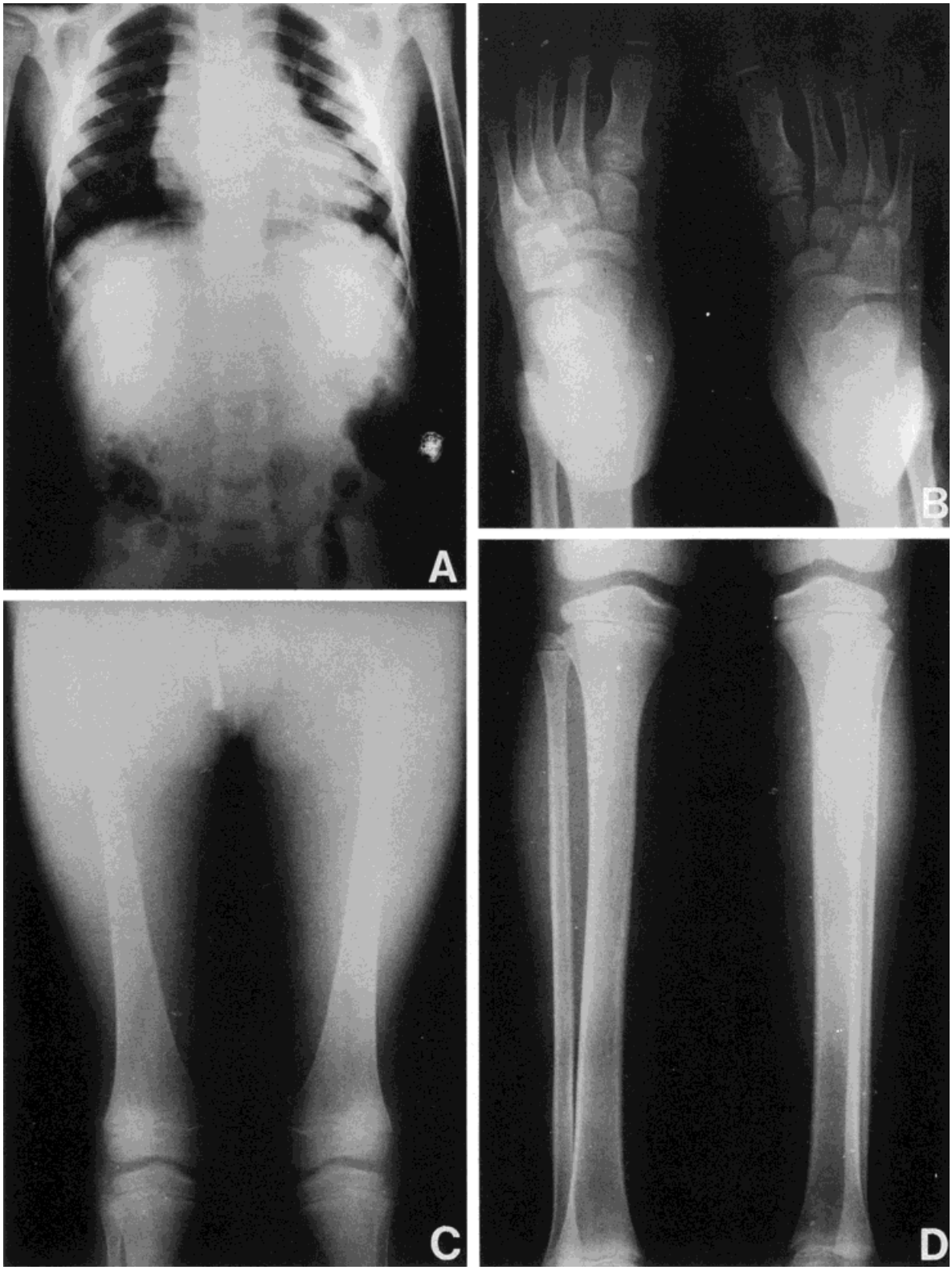

Fig. 2. Patient A, X-rays at age 8 years. Note: (**A**) Global cardiomegaly, (**B**) broad first metatarsal, with short and broad distal phalanx, and (**C** and **D**) broad metaphyses and medullary canals of the long bones.

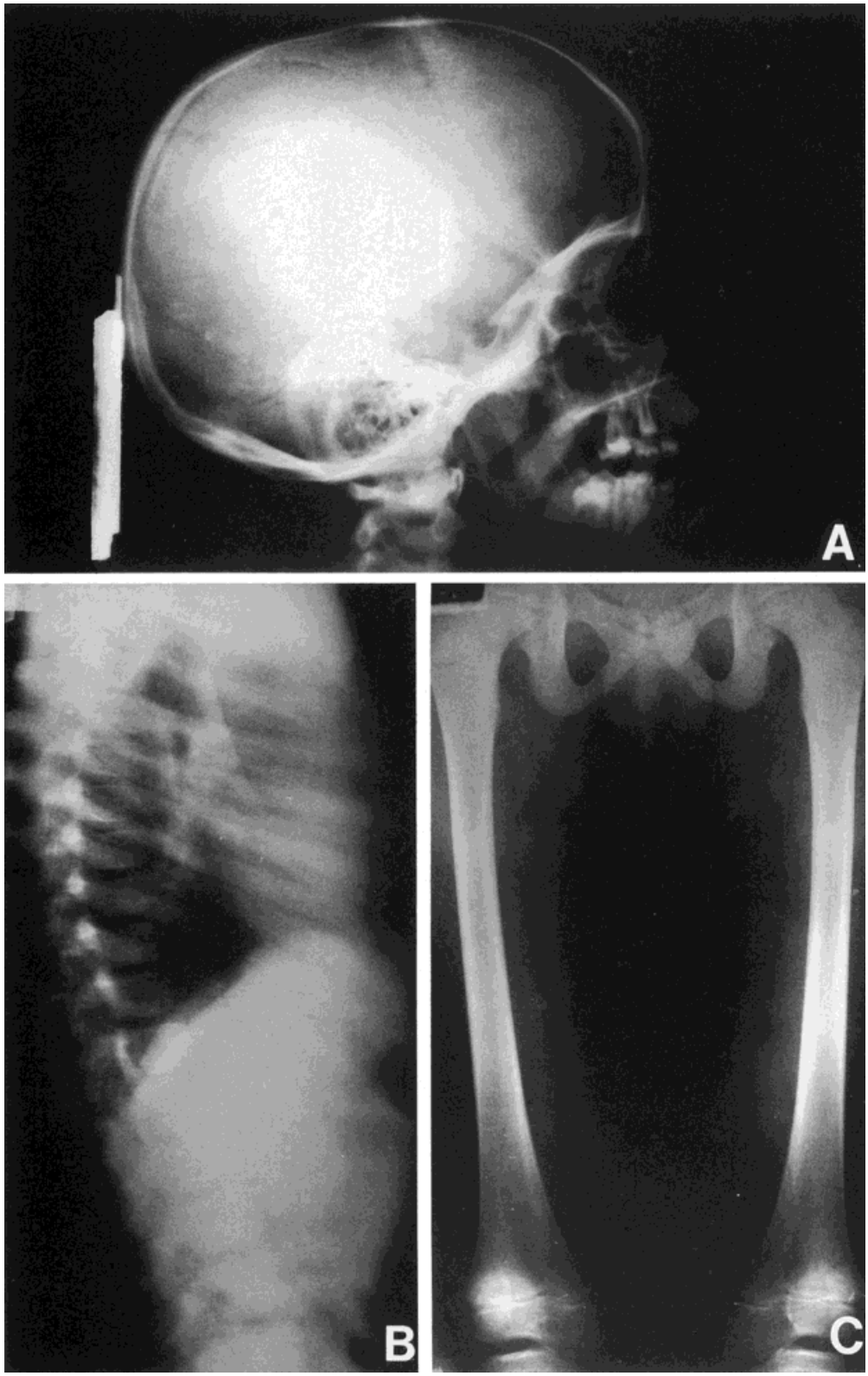

Fig. 3. Patient A, X-rays at age, 10 years. Note: (**A**) Verticalized posterior fossa; (**B**) narrow thorax and ovoid-shape vertebral bodies; (**C**) the medullary canals and metaphyses more broadened.

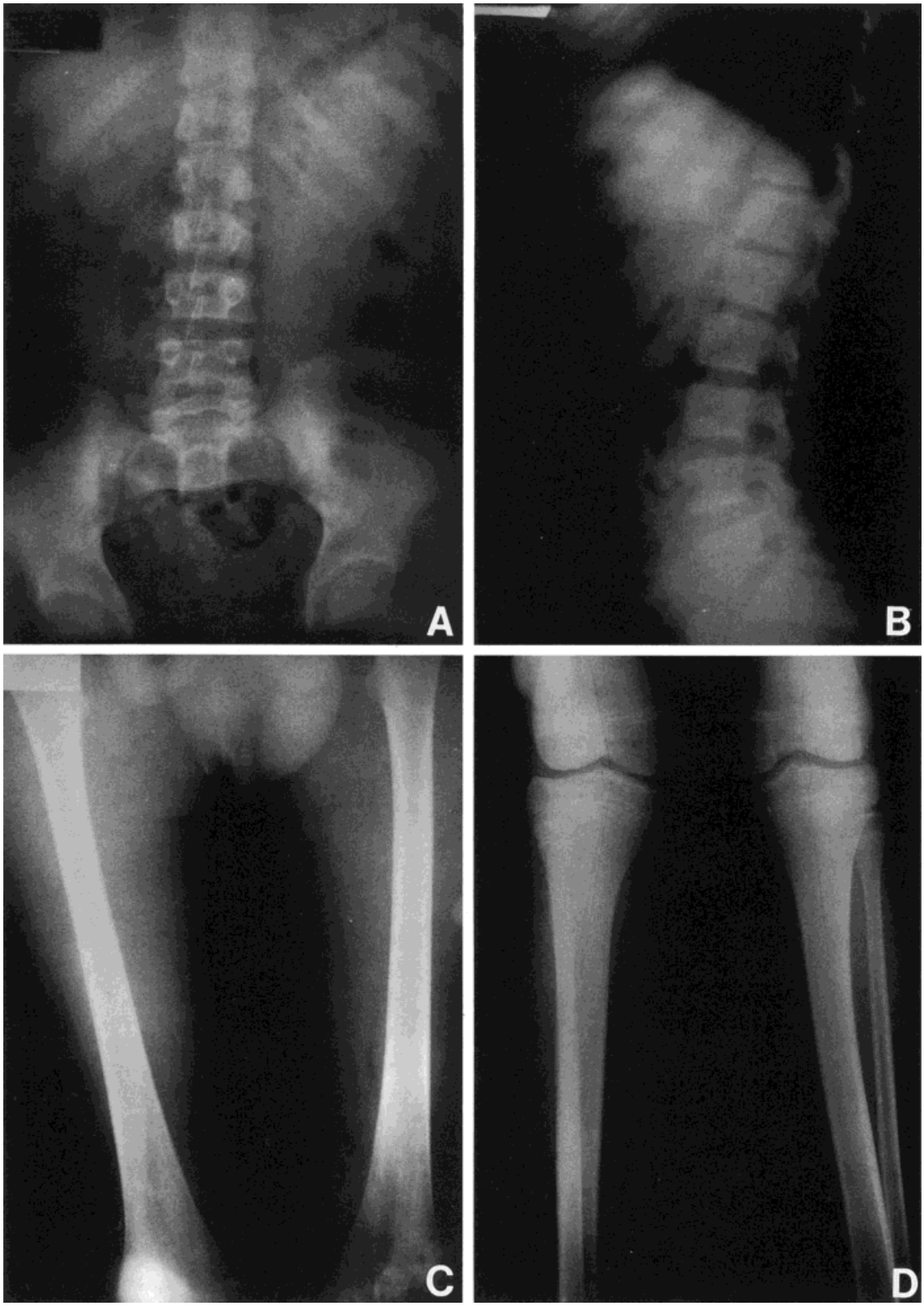

Fig. 4. Patient A, X-rays at age, 15 years. Note: (**A**) Broad ribs; (**B**) cuboid-shape vertebral bodies with irregular articular surfaces; (**C** and **D**) broad metaphyses and medullary canals.

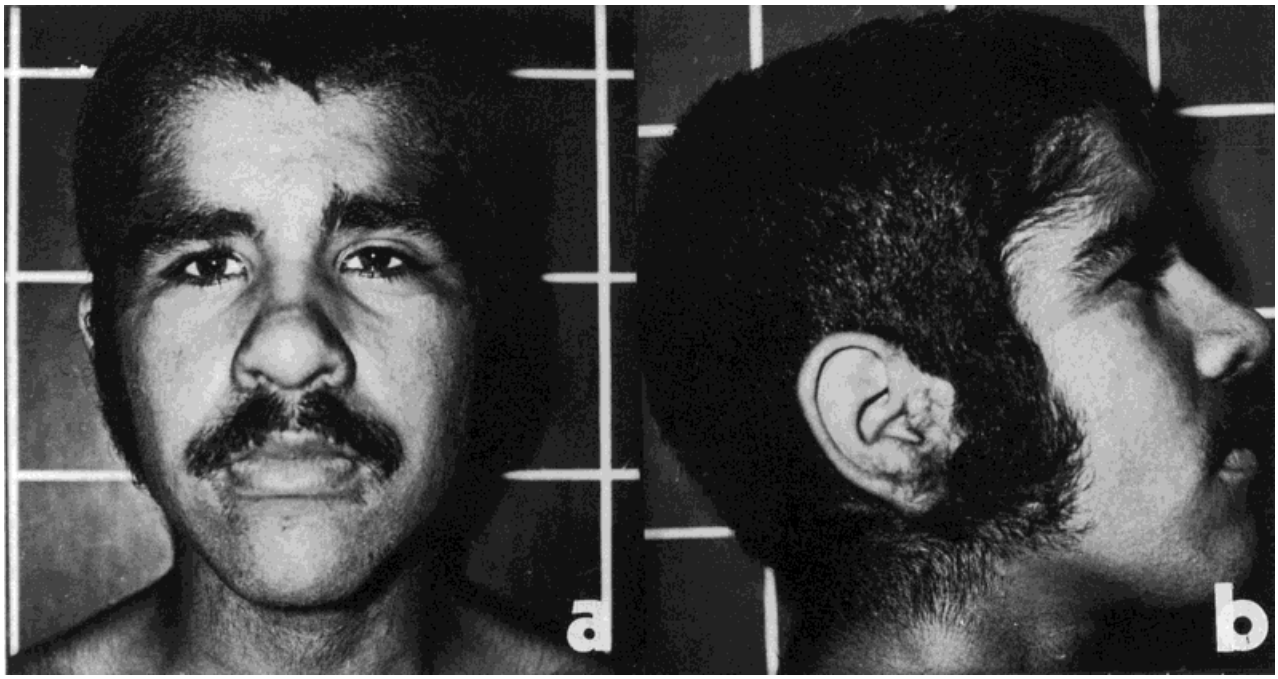

Fig. 5. Patient B at age 16 years. **a, b:** Close-up of the face; note excessive hairiness on forehead, eyebrows, eyelashes and moustache and an increase in preauricular hairiness, which extends to the nape on the neck.

nose, hairy external ears, large hands and feet, Tanner IV genitalia.

Oral examination showed permanent dentition, Angle's Class I at the level of the right canine; he also showed diastema between the lateral incisors. There was an open bite of 10%, crossing from the canine to the central incisor of the right side. The upper lateral incisors were smaller than normal. The cardiological evaluation and echocardiography gave normal results. The laboratory examination, including routine blood and urine tests, and screening tests, and screening tests for metabolic defects, showed normal results.

The radiological findings are summarized in Table III. As in Patient A, radiological follow-up was done, showing cuboid-shape vertebral bodies and "Erlenmeyer-flask" appearance of the long bones, which were not as evident at earlier ages; at puberty, metaphyseal flare mainly of the tibiae, was striking.

The parents were nonconsanguineous, 20 (mother) and 43 years of age at the propositus' birth. Both were clinically healthy, as were two sisters and brother.

Patient C

The proposita, age 6 years 3 months (Fig. 7), was the product of the mother's tenth term pregnancy with a prolonged delivery. Birthweight and length were not recorded. At birth, large eyes, thick eyebrows, curly eyelashes, and abundant hair all over the body were noticed. At 1 month of age, the hairiness became more noticeable, mainly on the arms, face and back, and turned lighter and thicker. Psychomotor development was delayed, with neck and trunk control at 11–12 months, gait and language at 18 months, and sphincter control at 24 months. The psychological evaluation at age 3 years showed a developmental quotient of 2 years and 10 months. The physical data are summarized in Table I; clinical data are in Table II.

Oral examination showed complete dentition without any abnormality. The cardiological status and an echocardiogram were normal.

The radiological findings are summarized in Table III (see Fig. 8). As in the other cases, radiological follow-up beginning at 3 months showed that broad medullary canals as well as an "Erlenmeyer-flask" appearance of the long bones became more evident at increasing age; accelerated bone age was also observed. The laboratory examination including routine blood and urine tests and screening tests for metabolic defects gave normal results.

The parents were healthy and nonconsanguineous, and aged 34 (mother) and 40 years at the proposita's birth. Three brothers and 5 sisters were described as healthy.

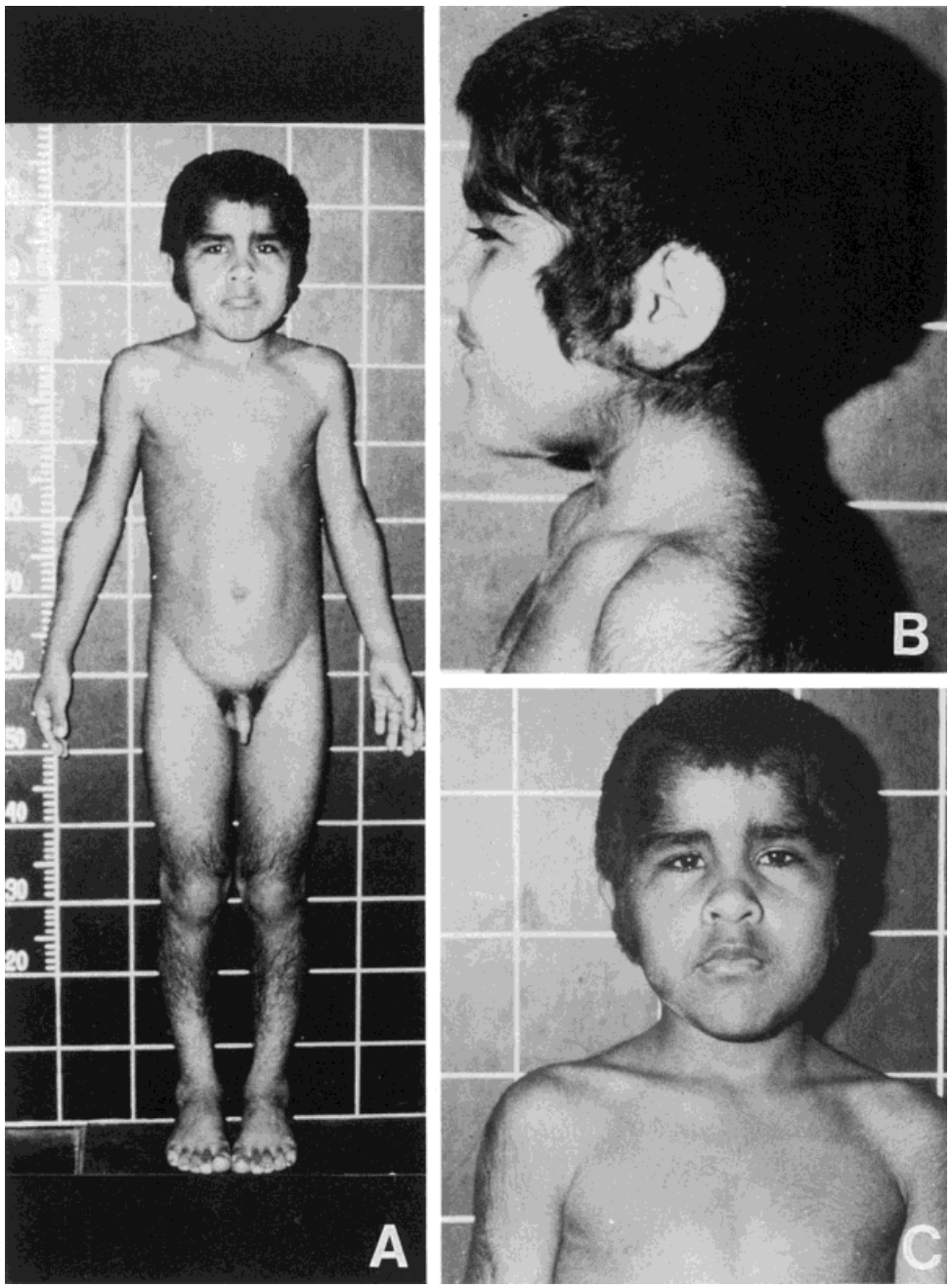

Fig. 6. Patient B at age 9 years. **A–C:** Distribution and characteristics of the hairiness are similar to other ages but more severe at earlier ages; pubic hair does not show a sexual distribution.

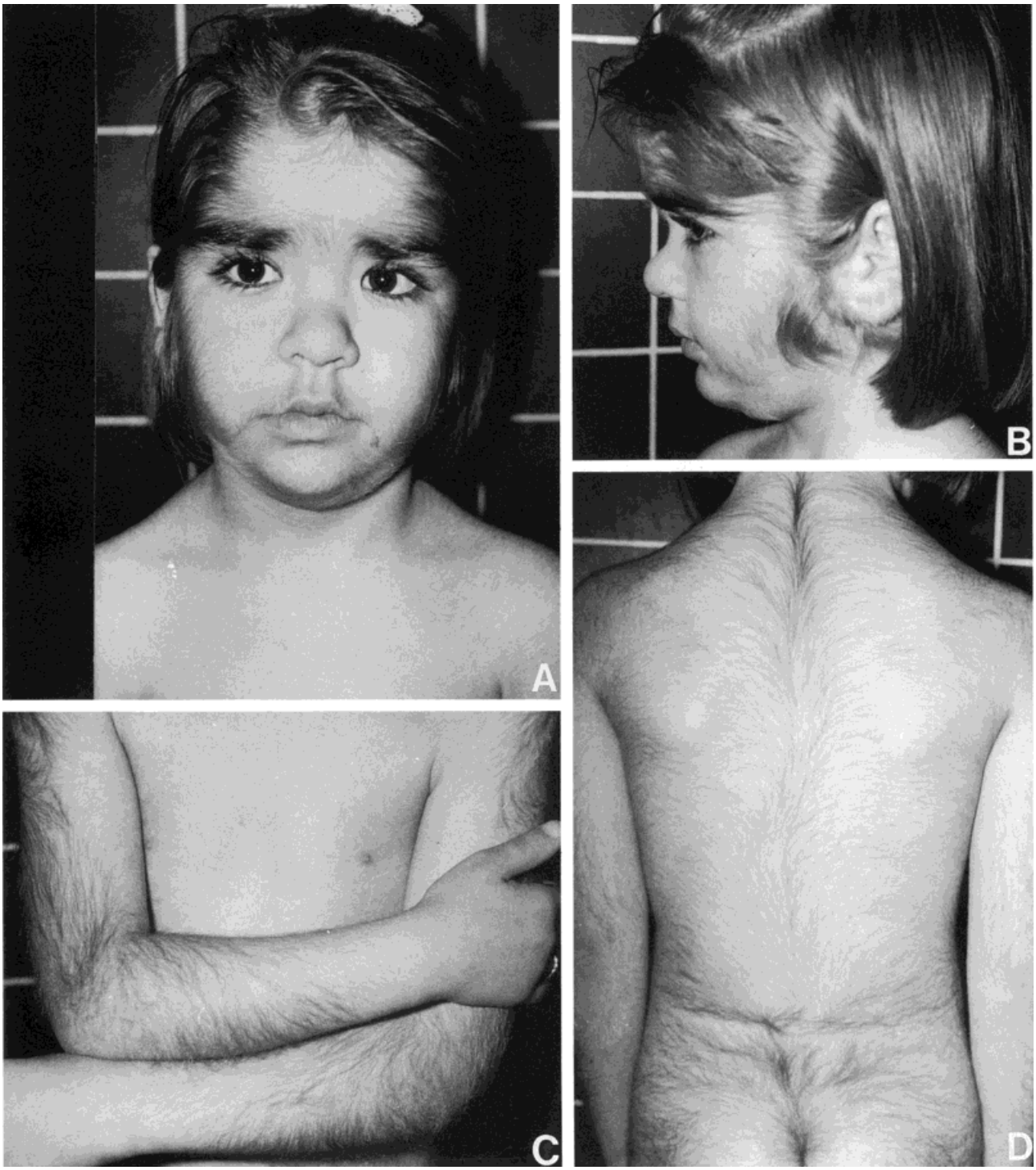

Fig. 7. Patient C at 6 3/12 years. **A, B:** Close-up of the frontal and lateral views, respectively. Note hypertrichosis on forehead (which continues to eyebrows, cheeks, moustache, and chin), synophrys, coarse face, abundant eyebrows and eyelashes, bilateral epicanthal folds, broad nasal bridge, and long philtrum. **C, D:** Hypertrichosis on forearms and back, which continues to the gluteal region.

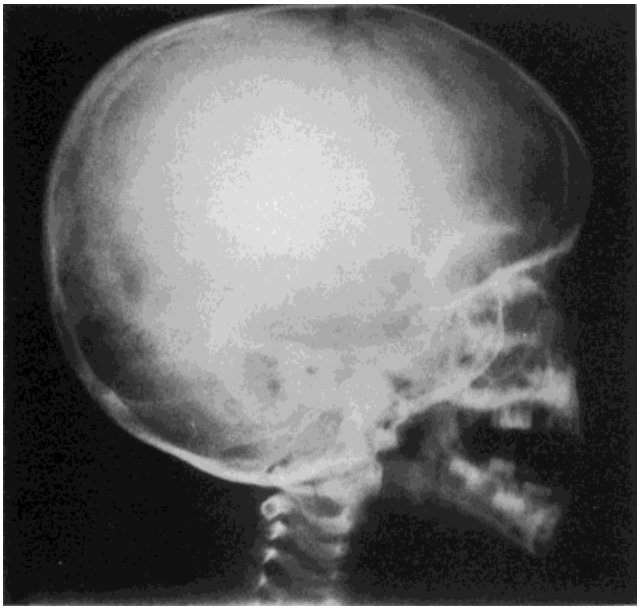

Fig. 8. Patient C, X-ray photograph at 4 years. Note disproportionate cranium, enlarged posterior fossa, and verticalized base of cranium.

Patient D

The proposita, age 3 years 6 months (Fig. 9), was the product of a second pregnancy of 35–36 weeks of gestation complicated by polyhydramnios; with delivery by repeat Caesarean section. Birthweight was 3,100 g. At birth, she presented with excess body hairiness persisting to date. The psychological evaluation showed a mental age of 7 months at age 11 months.

Physical data are shown in Table I. Additionally, there was macrodolicocephaly (Table II). No dental anomalies were observed. The cardiological evaluation was normal. Laboratory exams, as in the other cases, showed normal results.

The radiological findings are shown in Table III (Fig. 10). The bone age was normal. A cranial CAT scan showed cerebral atrophy. EEG evidenced diffuse encephalopathy.

The parents were healthy and nonconsanguineous and 30 (mother) and 29 years of age at the proposita's birth. A 4-year-old sister was normal.

Patient E

This is the brother (Case B) of the familial cases previously described by Cantú et al. [1982]. He was reevaluated at age 35 years because of pericarditis with effusion. The patient also had showed lymphedema of the right leg of few years before the pericarditis, which was detected during routine radiological studies. The effusion was voluminous (1,500 ml) and was surgically resolved.

The re-examination did not differ much from the original one. However, there were other interesting radiological findings (Table III and Fig. 11). The patient has developed a thoraco-lumbar rotoscoliosis. An echocardiogram showed concentric hypertrophy of the left ventricle with normal clinical evaluation.

DISCUSSION

The hypertrichosis-osteochondrodysplasia syndrome can be defined as a heritable disorder detectable at birth, with macrosomia and hypertrichosis, in addition to the findings described in Table I. Comparative analysis of the four new cases, added to the 4 patients described by Cantú et al. [1982], suggest that the clinical characteristics displayed in Table II are consistent in half or more of the patients. The congenital hypertrichosis changes from lanugo to postnatal hair and continues growing in length and quality. It is distributed all over the body, sparing only palms, soles, and mucosae. Macrocephaly is also a consistent clinical characteristic, present in two of the cases previously described. Mild mental retardation was observed in the present cases and also in one case in Cantú et al. [1982].

The radiological characteristics (see Table III) present in half or more of the patients were: wide posterior fossa in the skull, verticalized base of the cranium, narrow thorax, global cardiomegaly, broad ribs, platyspondyly, hypoplasic ischiopubic branches, small obturator foramen, bilateral coxa valga, broad medullary canals, long bones with an "Erlenmeyer flask" appearance, generalized osteopenia, bands of growth arrest, short distal phalanx of the thumbs, short and broad distal phalanx of the 1st toes, delayed bone age, and hypertrophy of the 1st metatarsals.

Findings in less than half of the patients were: ovoid-shape vertebral bodies, evidenced in Patients A and B at 10 and 12 years of age, respectively, becoming cuboid-shape in both after puberty. These findings are similar to those described by Cantú et al. [1982]. In contrast, irregularities on the articular surfaces of the vertebral bodies observed in Patients A, B, and E appeared after puberty. The "Erlenmeyer flask" appearance of long bones observed in patient C was evident as early as 4 months of age. At this age, metaphyseal flaring was not so noticeable.

Concentric hypertrophy of the left ventricle, present in patients A and E, apparently develops after puberty. Primary lymphedema and pericarditis with effusion, observed only in patient E, also occurred postpubertally. Characteristics that could

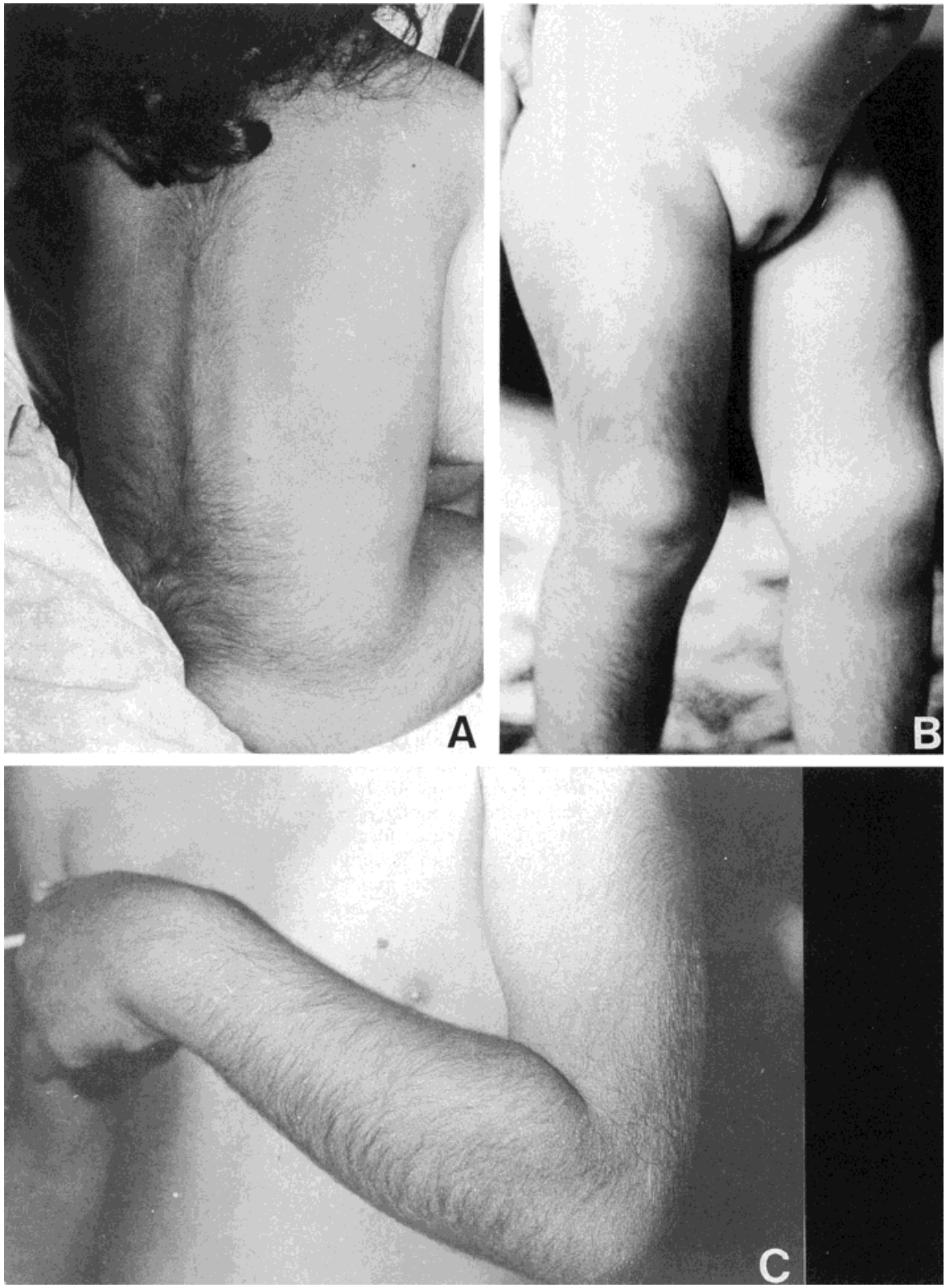

Fig. 9. Patient D. Note: (**A**) hypertrichosis of the back and gluteal region, (**B**) legs, (**C**) arms and forearms.

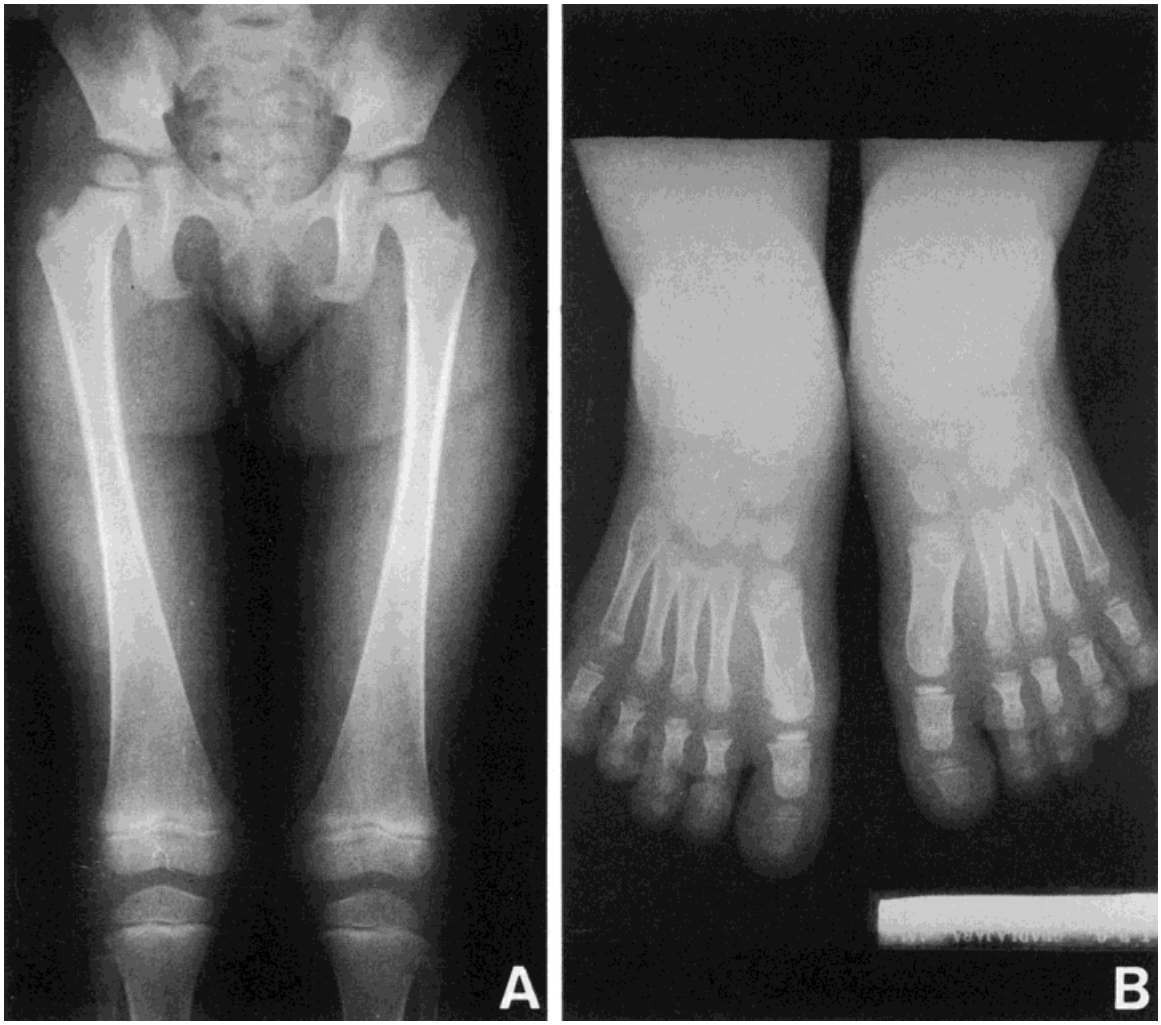

Fig. 10. Patient D, X-rays. **A:** Bilateral coxa-valga, long bones with an "Erlenmeyer-flask" appearance. **B:** Broadened first metatarsal and short distal phalanx of the first toes.

appear at puberty or later include: concentric hypertrophy of the left ventricle as well as cuboid-shape vertebral bodies with irregularities of the articular surfaces.

From the genetic point of view, although an autosomal recessive inheritance was first suggested [Cantú et al., 1982], the absence of parental consanguinity and the fact that 6 cases are sporadic indicate uncertainty in the presumed pattern of inheritance.

In the differential diagnosis, other conditions with hypertrichosis should be considered, including hypertrichosis universalis [Beighton, 1970; Danforth, 1925; McKusick, 1994], X-linked congenital generalized hypertrichosis [Maciás-Flores et al., 1984], a form associated with retinal dystrophy [Jalili, 1989], another associated with lid agenesis, mild mental retardation, and macrostomia [Cesarino et al., 1988], a new syndrome with cataract and mental retardation [Temtamy and Simbawy, 1992], another new syndrome with hirsutism, skeletal dysplasia, multiple congenital anomalies, mental retardation and uric acid metabolism disorder [Wiedemann et al., 1993], and that caused by Minoxidil [Patrinos et al,, 1987].

Whether in this condition the hypertrichosis is a consequence of an atavistic mutation, as proposed by Cantú and Ruiz [1985] to explain X-linked congenital generalized hypertrichosis remains to be elucidated.

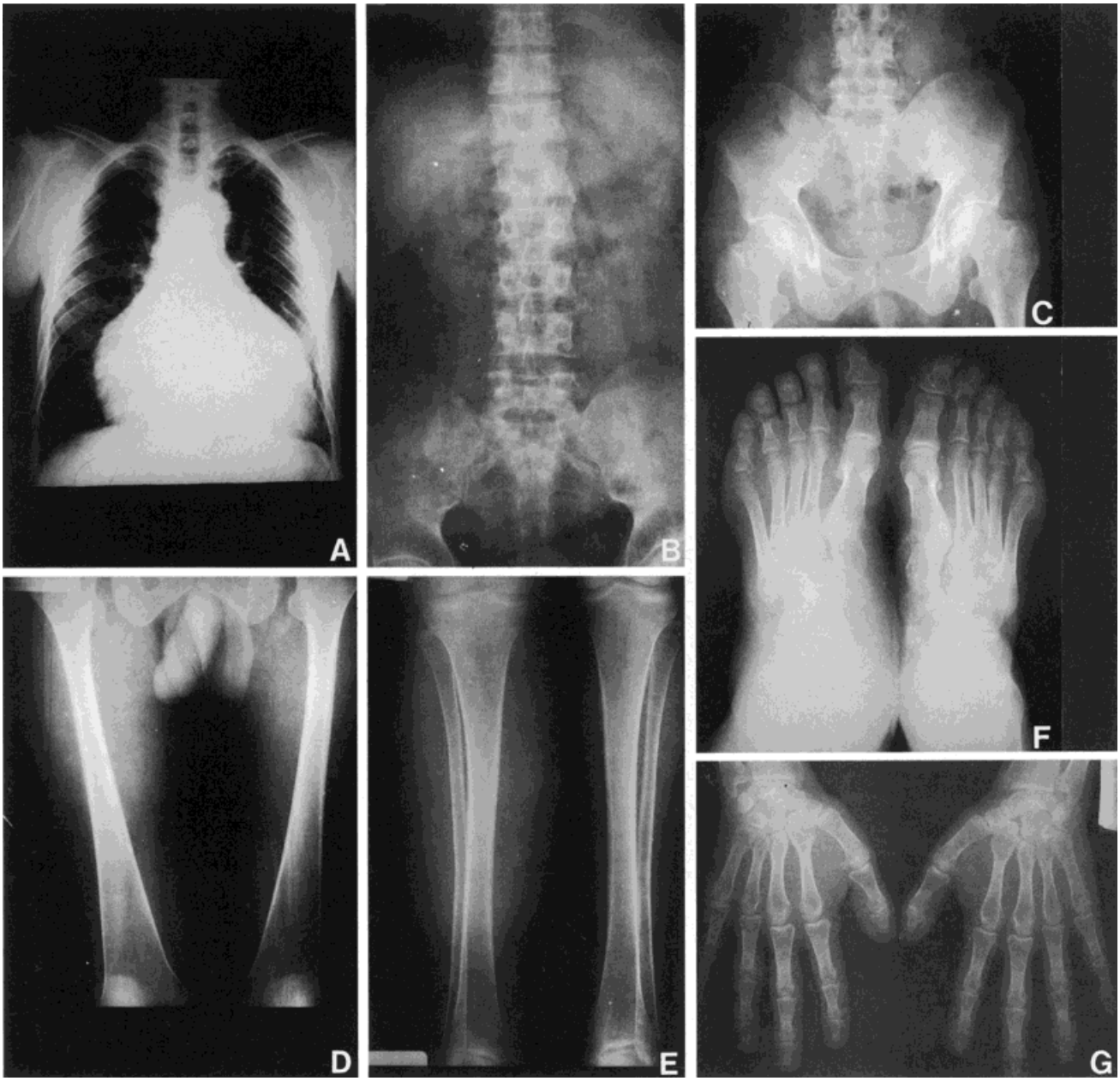

Fig. 11. Patient E, X-ray photographs at 35 years. **A:** Narrow thorax and pericarditis with effusion. **B:** Platyspondyly, cuboid vertebral bodies. **C:** Hypoplastic ischiopubic branches, small obturator foramen, bilateral coxa valga. **D, E:** Long bones with "Erlenmeyer-flask" appearance with broad medullary canals. **F:** Broadened first metatarsals with short and broad distal phalanx. **G:** Short distal phalanx of the thumbs.

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